DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 23, 2011 has been entered. Claims 1, 8-10 and 12-18 are under examination. All other pending claims are withdrawn from consideration being drawn to non-elected subject matter.

Response to Amendment

2. The rejection of claims 1, 3, 4, 8-12, 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Horsburgh *et al.* (US Patent 6,277,621 B1, "Horsburgh") is either moot in view of cancelled claims or withdrawn in view of Applicant's amendment regarding the recombinant protein dependent recombinant sequence component which is not taught by Horsburgh.

Likewise, the rejection of claims 13, 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Horsburgh *et al.* (US Patent 6,277,621 B1, "Horsburgh") in view of WO00/50603 (abstract, "WIPO abstract") is withdrawn.

The rejection of claims 7 and 16 under 35 U.S.C. 103(a) as being unpatentable over Horsburgh in view of Mori *et al.* (200802266") is moot in view of those claims being cancelled.

Claims Summary

3. The claims are drawn to a recombinant varicella-zoster virus (VZV), also known as human herpes virus type 3, HHV-3, comprising a bacterial artificial chromosome (BAC) vector sequence that is inserted into a non-essential region of a VZV genome. The insertion is in the ORF of gene 13, a non-essential gene. Note that "the region in the ORF of gene 13" is the elected species; see the remarks filed by Applicant on March 3, 2009.

Also claimed are pharmaceutical compositions and vaccines containing the recombinant VZV. The BAC vector sequence comprises a recombinant protein dependent recombinant sequences, selected from the group consisting of a loxP site, an FRT site, an attB, an attP site and a res site. The BAC vector comprises a selectable marker (*e.g.*, drug selectable marker, or GFP). In one embodiment, the BAC vector comprises SEQ ID NO: 7. The VZV genome is comprises sequences from a wild type strain, an Oka vaccine strain, or a mutant type strain. The genome has mutations in gene 62 (*e.g.*, substitution at position 2210 to G, 3100 to G, 3818 to C, 4006 to G).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8-10 and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, lines 2-3 indicate that the BAC vector sequence is inserted into a non-essential region or the flanking region of a non-essential region. Claim 1, lines 5-8 indicate that the non-essential region is the region flanking the ORF of gene 13. It is

unclear why, in lines 2-3, the vector sequence is inserted into a non-essential region or the flanking region, yet in lines 5-8, the only choice is a region flanking the ORF of gene 13. The elected species is "the region in the ORF of gene 13". Clarification and correction are required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8-10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horsburgh *et al.* (US Patent 6,277,621 B1, "Horsburgh") in view of Cohen *et al.* (PNAS USA, 1993, 90:7376-7380, "Cohen") and Mori *et al.* (US Patent Application Publication 20080226677, filed May 12, 2004, "Mori").

Horsburgh discloses a recombinant VZV virus comprising a BAC vector sequence (see col. 6, lines 1-17, col. 1, lines 50-54, 65-67; col. 3, lines 41-48; and col.10, lines 15-18). The encoded virus is attenuated (see col. 2, lines 2-9). The BAC is inserted into a non-essential region of the virus genome (see col. 6, lines 40-54). Selectable markers, such as drugs and GFP are suggested (see col. 11, lines 18-29; and col. 12, line 67). Horsburgh suggests that the expression system can be used to generate attenuated or mutated viruses for purposes of immunization (see col. 5, lines 4-30).

Claims 11 and 12 require the presence of sequences from a wild type strain of VZV or a mutant type strain of VZV. The claims language indicates that only some sequences from the

viral strains need be present. Since there are no particular sequences identified that must be included in the VZV genomes, it is reasonable to expect that any VZV genome will meet the limitations of these claims.

Although Horsburgh does not specifically suggest that the viruses be used as pharmaceutical compositions or vaccines, note that there are no additional components to render the actual contents of the composition distinct from a composition comprising the virus. Horsburgh's viruses are expected to be in some sort of culture or medium during their production and storage, which qualifies as a composition. Although the claims call the composition "pharmaceutical compositions" and "vaccines", the only contents of those compositions are the viruses, which is what Horsburgh teaches.

Horsburgh teaches that the BAC is inserted into a non-essential region of the virus genome (see col. 6, lines 40-54), but does not indicate which non-essential region. One of ordinary skill in the art would have been motivated to use any known non-essential region of VZV to insert the BAC, such as the ORF of gene 13, thymidylate synthetase. Cohen discloses that the VZV thymidylate synthetase (ORF of gene 13) is not essential for replication and is therefore non-essential (see abstract). One would have had a reasonable expectation of success in view of Cohen's recovery of virus particles.

Regarding the presence of a recombinant protein dependent recombinant sequence, Mori discloses the use of BAC vectors to express viral genes, as well as the use of recombinant protein dependent recombinant sequences as instantly claimed (see paragraph [0102] on page 8, and paragraph [0209] on page 26, for example). One would have been motivated to use such sequences in order to control the site of recombination. With regard to the BAC vector sequence

comprising SEQ ID NO: 7, although Horsburgh does not disclose this particular sequence, it would have been obvious to have used any other available BAC vector sequence, such as the sequence taught by Mori as SEQ ID NO: 401 (100% identical to Applicant's SEQ ID NO: 7). One would have had a reasonable expectation of success because Mori uses human herpesviruses (types 6 and 7) with the BAC vector sequence.

Regarding the particular strain and particular mutations embodied in claims 13-15, Horsburgh does not disclose these limitations. However, these mutations are attenuating mutations of a VZV Oka strain, as disclosed by Cohen. Cohen discloses particular mutations in gene 62 of VZV Oka strain that render the strain attenuated and useful as a vaccine. Given that Horsburgh suggests that genomes of live, attenuated viruses can be expressed from the BAC construct, it would have been obvious to have used the Oka strain with its attenuating mutations with a reasonable expectation of success because of its known attenuation and use as a live, attenuated virus vaccine (see Cohen, abstract).

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that there are clear structural and functional differences between HSV and the instantly claimed VZV. Applicant argues that Horsburgh is not applicable to live, attenuated recombinant VZV using non-essential gene regions, rather, Horsburgh is directed to artificial chromosome constructs containing HSV sequences.
    - In response to Applicant's arguments, Horsburgh clearly suggests using attenuated viral coding sequences, including not only HSV, but also VZV (see col. 3, lines 41-48, and col. 2, lines 2-9).

- Applicant argues that Horsburgh describes recombination "in the ORF region" of a gene, while the instant claims are drawn to insertion of BAC sequences into "a region flanking" non-essential genes that does not disrupt the gene so that it remains functional. Applicant also points out the Horsburgh's UL13 is not the same as VZV gene 13, as does Kazuhiro Nagaike in the declaration filed under 35 CFR 1.132 on May 23, 2011. Kazuhiro Nagaike points to Gomi *et al.* (*J. Virology*, 2002, 76(22):11447-11459), which points to Cohen *et al.* (PNAS USA, 1993, 90:7376-7380) in the bibliography, as evidence that the inventors discovered that VZV 13 is a non-essential gene.
    - In response, the Office appreciates Applicant pointing out that HSV UL13 is not the counterpart of the VZV gene 13. On this point, the declaration is persuasive. Accordingly, the rejection no longer asserts that Horsburgh teaches VZV gene 13, rather, Cohen *et al.* (PNAS USA, 1993, 90:7376-7380) is relied upon for that teaching.
    - With regard to the argument regarding flanking regions of non-essential genes, the Office reminds Applicant that the elected species is "the region in the ORF of gene 13". Thus, while Horsburgh does not teach inserting into the flanking region of the ORF of gene 13, this embodiment is not under examination at this point in prosecution. Applicant has not canceled the elected species from the claims, since the claims still recite, "wherein the BAC vector sequence is inserted into a non-essential region **or** the flanking region of a non-essential region" [emphasis added].
- Applicant argues, as does Kazuhiro Nagaike in the declaration, that the HSV vector of Horsburgh would be ineffective as a vaccine because the TK gene is disrupted in the

HSV vector produced by Horsburgh, and the safe use of HSV requires acyclovir to guard against uncontrolled viral proliferation. Applicant argues that the VZV Oka strain is an attenuated, live vaccine whose safety is guaranteed without the use of acyclovir.

- In response, the claims are directed to constructs comprising VZV, not HSV. Therefore, Applicant's arguments, and Kazuhiro Nagaike's statements relating to HSV are not relevant. The fact remains that the claims are directed to a live, attenuated VZV comprising a BAC, which is what is taught in the prior art. Therefore, the invention remains rejected as obvious.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 8-10 and 12-18 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 11-17, 24 and 25 of

copending Application No. 12/094,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed subject matter of the co-pending application falls within the scope of the recombinant BAC instantly claimed. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. In the remarks filed May 23, 2011, Applicant requests that this provisional rejection be held in abeyance until allowable subject matter is indicated.

Applicant also remarks that it is improper for the Office to maintain a provisional obviousness-type double patenting rejection based on claims that have not been allowed or issued in a patent. Applicant also states that the instant claims should be examined on their merits. In response to Applicant's remarks, it is proper for the Office to maintain a provisional rejection because the claims of either case have not been allowed or patented; this is the nature of the rejection being "provisional". As the instant claims are still rejected for other reasons besides the provisional rejection, the provisional rejection stands because there is no allowable subject matter. Further, the instant claims have indeed been treated on the merits because they have been under examination since at least the first Office action on the merits mailed September 30, 2010.

Conclusion

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACY CHEN whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648